PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 31287	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/IL2006/000483	International filing date *(day/month/year)* 20.04.2006	Priority date *(day/month/year)* 03.11.2005
International Patent Classification (IPC) or national classification and IPC INV. B01J19/00		
Applicant SENG ENTERPRISES LIMITED		

1. This report is the International preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand 2007-08-16	Date of completion of this report 28.11.2007
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2006/000483

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-45 as originally filed

   Claims, Numbers

   1-43 as originally filed

   Drawings, Sheets

   1/27-27/27 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2006/000483

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	29-34
	No:	Claims	1-28,35-43
Inventive step (IS)	Yes:	Claims	29-34
	No:	Claims	1-28,35-43
Industrial applicability (IA)	Yes:	Claims	1-43
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents (**see in particularly the passages referred to in the International search report**):

D1: WO 2004/113492 A (MOLECULAR CYTOMICS LTD; DEUTSCH, MORDECHAI; HERZBERG, MAX; TIROSH, REU) 29 December 2004, cited in the application

D2: WO 03/035824 A (BAR-ILAN UNIVERSITY; DEUTSCH, MORDECHAI) 1 May 2003, cited in the application

D3: US-A-5 506 141 (WEINREB ET AL) 9 April 1996

2 Attention is drawn to the fact that "picowell" is not a generally used term in the trade or acknowledged in this technical area (Rule 10.1(e) PCT). The description defines this term on page 4 line 21-23, e.g. "*a small well-shaped feature (including cavities, dimples, depressions, tubes and enclosures) configured to localize cells in well-defined locations on the bottom surface of a vessel*". Given the definition provided, a "picowell" is not a new feature as such. Furthermore, the term covers many possibilities.

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of independent claims 1 and 5 is not new in the sense of Article 33(2) PCT:

The document D1 discloses a method and a device for holding living cells for the purpose of studying them, said device comprising a carrier having several wells on surface. When a cover slip is placed or integrally formed with over carrier 12, fluid channels 16, matrix of wells 18 and reservoir 20 are sealed forming channels that allow transport of fluids and reagents to cells held in matrix of wells 18. The wells are configured to hold one or more cells and are preferably individually addressable both for examination and manipulation. The suspended cells are allowed to "settle" into individual wells or matrix of wells, said term not necessarily meaning that the cells

sink.
In detail, a transparent carrier 68 with a well matrix 18 is provided including a matrix of hexagonally packed knife-edged hexagonal wells having a plurality of protuberances emerging from the area between the wells. Transparent carrier 68 is mounted in a holder 42, where cover slip 52 is held in place by gasket 54. An inlet flow device is in communication with the fluid channels of transparent carrier 69 through capillary tubes 30.

Generally, when the cell is submitted to the well suspended in a fluid (such as a low temperature liquid agarose), the fluid is subsequently gelled, e.g. no longer floating upon study. As an alternative however, as shown in figures 7A and 8A, the suspended cell settles and is held in enclosures 60. Here the gellable fluid is optional only.

In respect of the independent claim 5 and the scope thereof, attention is additionally drawn to item VIII point 4.1 below.

3.2 D1 does not mention any "force applicator" for maintaining a movable wall secured to the chamber as described by independent claim 35 on file.

3.3 On page 2 D1 teaches that "Although exceptionally useful for the study of large groups of cells, multi well micro titer plates are not suitable for the study of individual cells or even small groups of cells due to the large, relative to the cellular scale, size of the wells. Generally, cells held in such wells float about a solution in the wells and are not easily found for observation." In fact, claim 29 on file does not define that a single cell is to be held in each "picowell"; on the contrary, it defines a method for studying cells where **at least** one cell is introduced into a chamber.

Attention is drawn to the description, p. 20 l. 17-21. If claim 29 is to be interpreted such that the chamber, when filled with one cell per well, is turned "upside down" in respect to its initial position (e.g. the top wall with the bottom surface holding the well -section a of the claim- is oriented such that the bottom surface is then making up the down side of the device -section d of the claim- then D1 does not disclose such a method.

3.4 The independent claims 29 and 35 would therefore describe subject matter being new over the disclosure of D1 (Article 33(1)(2) PCT).

4.1 The present application does also not meet the criteria of Article 33(1) PCT, because the subject-matter of independent claims 1 and 5 is not new over D2 in the sense of Article 33(2) PCT:

D2 describes a transparent individual cell processor device for assessing single, individual living cell or group of cells at identifiable locations, a TCC ("transparent cell chip"). The device has a mechanism to direct the cells and force them to enter into the wells or to place them in the wells directly or to exit or remove them from the wells. The well's "coin" 30 may be made of porous material.
Furthermore, cell morphology, cell activity, cell physiology, cell metabolism, cell affinity and viability and changes that may occur as result of presence or absence of contact with other cells and/or particular biologically active materials are measured and assessed. An arrangement where the cells are placed on the bottom surface of a top wall is shown in figure 39 and described on page 31.

It is at least hinted that the cells can be suspended upon examination since D2 takes into account the refractive index of the suspending media (p. 65 to p. 67).
"Morphological quantification of micron objects" is explicitly mentioned on p. 66.

In respect of the independent claim 5 and the scope thereof, attention is drawn to item VIII point 4.1 below.

4.2 Claim 56 of D2 defines a detachable holder unit which may be removed from the device, while holding the TCC, manipulated as an isolated unit, and may be re-attached to the device, when needed. In the present description (page 6 line 11-15) the Applicant admits that, in fact, this corresponds to "movable wall" in the sense of the present invention. In this context, particular attention to the wording of claim 35 currently on file is required -it is the wording of the claim that defines the scope.

Claim 35 on file additionally defines an unspecified "force applicator" in combination with functional features (e.g. "configured to removably apply....to retain said movable

wall to the chamber") for maintaining the wall in place. There is no technical indication in this apparatus claim 35 how this is to be achieved. There appears to be no reason why the wall according to D2 should not be held in place either.

The Applicant is reminded that it is the wording of the claims that is decisive for their interpretation.
At the current stage of the proceedings claim 35 does not appear to disclose any subject matter being novel over D2. Claim 29, interpreted in the light of the description, must be deemed novel over D2 for the same reasons as for D1 (Article 33(1)(2) PCT)(see §§ 4 above).

5.1 D3 teaches that in the prior art studying floating cells is known *per se* (col 1 l. 56 - col. 2 l. 4): "...In this method cells float upon an isotonic solution of known density, osmolarity and viscosity. This configuration is subjected to acceleration forces by centrifugation at a given temperature and acceleration. The cells, having a specific weight greater than that of the solution sink. Those having the specific density of the solution are suspended in it, and those with a specific density less than that of the solution float above it...". This principle is however taught in respect of morphology studies and is not applied in D3, where the invention lies in studying stationary cells in an **apertured** holder (e.g. not floating cells).

5.2 Thus, from D3 a process and device for studying individual, living cells in large numbers is known, said teaching comprises applying cell suspensions to a matrix having a regular array of indentations or pockets, each of which serves as a cell container. The array of single cells can be treated automatically or manually with nutrients and additives, such as chemotherapeutics and antibodies in controlled amounts and the effects of such treatment can be observed.

As can be seen from for example fig. 3, a flow director 16 ensures that the solution contacts the cell carrier 1, which is located on a bottom surface of a top wall of the chamber.

The **apertured** cell holder 10, which is the top of the flow chamber, is removably mounted upon a central part 11 (fig. 2A) of the flow chamber, e.g. at least one wall is

removable. The central part 11 defines a plurality of channels 12, each being connected at both ends to one of a plurality of tubes 13 for supplying and discharging a desired solution.

5.3 The present application meets the criteria of Article 33(1) PCT, because the subject-matter of independent claims 1, 5, 29 and 35 is new over D3 in the sense of Article 33(2) PCT.

6. Inventive step

6.1 The principle of selecting a media such that a cell either floats, sinks or remains suspended is known as such, which is also evidenced by D3 (see above). Making use of a known principle cannot be considered as involving an inventive step as such. It is also known to study individual living cells in "picowells" as proven by D1 to D3. D1 and D2 describe cells held in a media.

Although D3 does not recommend the morphology studies as referred to as prior art in this document, the skilled person knows that it is possible to select the media such that the cells float.
D1 also acknowledges that cells are known to float on microtiter plates, but due to the size of the known devices, the cells float about and are hard to find for detection (p. 1 l. 29-33).

6.2 In respect of the prior art cited it appears that the problem underlying the invention resides in making available a special device capable of maintaining an individual floating cell and making use of this device for studying a single floating cell. In addition to the novelty objection made above, the independent claims 1 and 5 do not clearly and unambiguously define any inventive features solving this problem, in particularly since "picowells" and "studying floating cell" are known as such. The location of the cells in the chamber - a "bottom surface" of a "top wall" (a definition additionally depending on from which angle the device is seen) as defined by claims 1 and 5 on file is a matter of design to the skilled person, said activity not involving any inventive skills.

Even if claims 1 and 5 would define new subject matter, the present application does additionally not meet the criteria of Article 33(1) PCT, because the subject-matter of said claims does not involve an inventive step in the sense of Article 33(3) PCT.

6.3 At the present stage of the proceedings and in the light of the description, it would appear that claim 29 describes subject matter involving an inventive step since no document cited proposes studying single cells by turning over a well bearing device in which the cell floats.

The present application appears to meet the criteria of Article 33(1) PCT under the above provision, because the subject-matter of the independent claims involves an inventive step in the sense of Article 33(3) PCT.

7. Dependent claims 2-4, 6-28 and 36-43 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (see D1 and D2).

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the background art disclosed in the document D3, e.g. the fact that living cells are studied in the manner described by D3, is not mentioned in the description, nor is this document identified therein.

2. The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

3. The unit "microns" employed throughout the application is not recognized in international practice, contrary to the requirements of Rule 10.1(d) PCT. Instead "micrometers" or "µm" should have been used.

4. There is a clerical error on page 15 line 26 "the chamber the chamber".

Re Item VIII

Certain observations on the international application

1. Although claims 1 and 29 as well as claims 5 and 35 have been drafted as separate independent claims, they relate effectively to the same subject-matter and differ from each other only with regard to the definition of the subject-matter for which protection is sought. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT. The application should have shown a set with two independent claims only, e.g. a method claims and an apparatus claim.

2. Claim 35 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statement does not enable the skilled person to determine which technical features are necessary to perform the stated function: "configured to removably apply....to retain said movable wall to the chamber") for maintaining the wall in place (also compare with point V, § 4.2 above).

3. The term "picowell" used throughout the application is unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter unclear, Article 6 PCT (also compare with point V, § 2 above). Unambiguous terminology should have been used instead.

4.1 Claim 5 is not necessarily related to claims 1 and 29 since there is no technical feature relating to the fact that cells must be floating. An essential technical teaching is therefore missing here.
Additionally, the expression "for the study of living cells", the intended use of the device, is not restricting the scope of the claim.
Furthermore, term like "top" and "bottom" can only be considered as limiting if there is only one logical manner in which the device is to be seen. This claim merely defines a device comprising a chamber and a well supported on a carrier inside the chamber. Claim 5 is for these reasons considered unclear (Art. 6 PCT).

4.2 Claim 35 also comprising the expression "for the study of living cells", e.g. the intended use of the device, which is not restricting the scope of the claim (Art. 6

PCT).

5. In the description (page 11 line 13-15) the Applicant states that the cells and the medium are entered separately. There is no mention of this in the independent claims. Thus, an essential feature is missing for which reason the claims do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

6. Several terms (such as "Annexin V" and others on page 20, "Olympus BX61" on page 21, "Protanal LF120" on page 45, adhesives "3051" and "3341" on page 46) employed in the description and appearing to be registered trademarks have no precise meaning as they are not internationally accepted as standard descriptive terms. Thereby unclarity is introduced. If these terms represent registered trademarks, they should have been acknowledged as such.

7. The vague and imprecise statements in the description on page 49 lines 17-28 imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them. Such statements should have been omitted.